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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,879	06/22/2000	MICHAEL GIESING	790076.401	6896

23364 7590 06/17/2005

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,879	GIESING ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26,27,29-37,44,52,54 and 61-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26,27,29-37,44,52,54 and 61-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed March 16, 2005. Currently, claims 24, 26-27, 29-37, 44, 52, 54, 61-66 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's response and the amendments to the claims. The action contains new grounds of rejection.

Priority

3. This application is a 371 of PCT/EP/98/05360, filed August 24, 1998. This application also claims priority to foreign document 197 36 691.0, filed August 22, 1997, however, a translation of this document has not been provided.

Applicant's request clarification from the Examiner regarding the reference to the priority document in the first paragraph. The examiner has not required or even requested a translation. The examiner has merely indicated that the translation has not been provided.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 24, 26-27, 29-37, 44, 54, 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditkoff et al. (Surgery, Vol. 120, December 1996, pages 959-965) in view of Schmitz et al. (US Pat. 6,190,870, February 20, 2001) in view of Hoon et al (US Pat 6,057,105, May 2, 2000) and Rimm et al. (US Pat. 6,197,523, March 2001).

Ditkoff et al. (herein referred to as Ditkoff) teaches a method of detecting circulating thyroid cells in peripheral blood. Ditkoff teaches that the tissue specificity of thyroglobulin gene expression and the sensitivity of RT-PCR analysis make detection of thyroglobulin detection useful. Postoperative peripheral blood was sampled. Thyroglobulin transcripts were detected in all 9/9 patients with metastatic thyroid cancer. 0/6 patients with benign thyroid disease and 0/7 normal volunteers. Ditkoff teaches that RT-PCR can be used to detect thyroglobulin mRNA in peripheral blood since the presence of these transcripts correlate with the existence of extrathyroidal disease. As

specifically taught in the methods section, blood was taken from patients/volunteers and total RNA was extracted, RT-PCR was carried out. This step of investigating takes place without previous removal of cancer cells from the plurality of cells (limitation of Claim 61ai). Further, the thyroglobulin gene is a nucleic acid which is essentially not expressed in a non-cancer cell in the body blood. For example, since thyroglobulin is secreted exclusively by the thyroid follicular cells, thyroglobulin is not expressed by neutrophils (i.e. a non-cancer cell in the blood)(limitations of Claim 61aii). As seen in the Table, it is clear that no control or benign thyroid disease patients showed any RT-PCR. Therefore, the ordinary artisan would have clearly recognized that the RT-PCR method of Ditkoff would be a technique that may be used to identify blood-borne tumor cells. Ditkoff further teaches that RT-PCR has been used to identify blood-borne tumor cells in several solid cancers including melanoma, prostate and neuroblastoma (page 964, col. 1).

Schmitz et al (herein referred to as Schmitz) teaches that tumor cells, particularly carcinoma cells are separated from peripheral blood by magnetic sorting (abstract). Specifically Schmitz teaches that cell samples may be contacted with antibodies which are directed to tumor antigens or lineage specific antigens are used to magnetically label the tumor cells. The labeled cells are separated from unlabeled hematopoietic cells by magnetic separation. The fraction of cell enriched for tumor cells is useful for quantitating the tumor cells and as a source of tumor cells for further characterization (col. 3, lines 30-45). Schmitz provides a long list of separation markers which may be cell surface antigens or located in the cytoplasm of the tumor cells. These markers

include EMA, HEA-125, C26, among many others (col. 4). Moreover, Schmitz teaches that tumor cells may be further characterized as to their phenotype by PCR, FISH in situ FISH competitive hybridization (col. 9, lines 4-6). The further characterization of these tumor cells allows for analysis of chromosomal translocations, oncogene expression, for example. Moreover, the expression of a number of proteins related to malignancy is of interest including oncogenes, erbB, myc, p53, drug resistance proteins, metatstic factors including metalloproteases, integrins, angiogenic factors and others (col. 9, lines 8-15)(limitations of Claims 33-36).

Additionally, Hoon et al. (herein referred to as Hoon) teaches methods of using multiple cancer makers provide increased sensitivity over methods using single cancer markers. Hoon teaches the prior art was limited by their ability to discriminate cancer cells from normal cells also carrying the marker, thus reducing the specificity and reliability. Hoon teaches that "tumor, heterogeneity has caused sensitivity problems where a single-specific marker has been employed" (col. 2, lines 23-29). Hoon provides a list of makers which are preferably detected, including tyrosinase, MAGE3, Cytokenatin 20 (col. 3, lines 15-30). Hoon teaches that the method is conducted at least twice on a given sample using at least two different primer pairs specific for two different specific markers (col. 4, lines 37-40). In a specific example, 15ml of blood was obtained from patients and collected in 5 sodium citrate tubes (col. 19, lines 22-23). The tubes were centrifuged and the buffy coat was removed. Analysis was performed on the blood specimens by PCR using multiple markers. The use of more than one marker can verify the presence of occult melanoma cells and significantly increase the

sensitivity of detecting melanoma cells that express few or no copies of tyrosinase mRNA (col. 21, lines 60-65).

Further, Rimm et al teaches Since approximately eighty two percent of all cancers are epithelial in origin (seventy two percent of which are fatal), epithelial cancer cells should be detectable in circulating blood. While the presence of epithelial cells in the circulating blood stream does not, by itself, prove malignancy, it does alert the cytopathologist to the greater likelihood of malignancy since epithelial cells are not normally seen in the circulating blood stream. In certain cases, however; such as after surgery; or as a result of physical trauma; or as a result of dental flossing, or in cases of prostatitis, for example, it is possible that non-malignant epithelial cells may be found in the circulating blood stream.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have combined the methods of Ditkoff and Schmitz because Hoon teaches that detection of multiple cancer makers provide increased sensitivity over methods using single cancer markers and Rimm discusses the limited nature of merely detecting foreign cells in the blood. Therefore, the ordinary artisan would have been motivated to have combined several cancer detection methods for several markers to increase sensitivity. The methods of Ditkoff and Schmitz both are directed to methods which allow detection of cancer-associated or cancer-specific markers within a body fluid, namely blood, with or without enrichment which indicates an increased risk for or the presence of a disseminated cancer cell. The method of Ditkoff detects amplification without the need for enrichment, whereas the method of Schmitz isolates cancer cells

and normal cells and subsequently performs analysis s to their phenotype by PCR, ELISA, FISH, in situ FISH, comparative hybridization, for example. The collection of two tubes of blood from a cancer patient or a patient suspected of having cancer and performing the analysis of both Ditkoff and Schmitz allows for the detection of multiple markers which increases sensitivity and increases the likelihood of early detection of cancer, as taught by Hoon. There are numerous reasons why it is advantageous to use peripheral blood including that it is less stressful for the patient and therefore may be performed on a routine basis together with other laboratory tests. Therefore, when blood is drawn from a patient having cancer or suspected of having metatstasis, several tubes may be collected with minimal discomfort or stress for the patient. The multiple tubes of blood may be used for a variety of laboratory tests including RT-PCR and cancer cell isolation. As specifically provided by Hoon, detection of more than a single cancer marker is strongly recommended to provide more sensitive and accurate results. Further, Rimm teaches that the presence of foreign cells in the circulating blood stream may be due to trauma, or other causes aside from disseminated cancer cells. Therefore, analyzing a single patients blood samples for more than one known cancer marker would have the expected benefit of minimizing the stress and pain inflicted on the patient while simultaneously obtaining sensitive and meaningful results to determine whether micrometastasis is present in the sample. Schmitz teaches numerous genes which are differentially expressed between cancer and normal cells, such that the ordinary artisan would be motivated to have selected any combination of such markers

depending upon the suspected form of cancer in which they are studying or select a combination which is more general to cancers generically.

Response to Arguments

The response traverses the rejection. The response asserts the art combination relies on unjustified overgeneralization of Hoon. The response asserts that Hoon is limited to use of multiple markers in a single sample. This argument has been considered but is not convincing because whether markers are detected in a single sample or whether the are detected in multiple samples from the same original starting material, i.e. blood would not change the teachings of Hoon. Hoon teaches that multiple markers may be used for verification, and increased sensitivity. Hoon teaches analyzing cells from buffy coat, Ficoll-hypaque gradient centrifugation, for example. Thus the teachings of Hoon are limited to any particular sample type. The teachings of Hoon have been broadly interpreted to encompass the concept that detection of two markers in samples is more sensitive and more desirable than only detecting a single marker.

The declaration of Professor Giesing has been thoroughly reviewed and considered, but not convincing. As provided in MPEP 716.02(a), "Evidence Must Show Unexpected Results." Further, "Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima

facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.)."

In the instant case, while the response asserts that the declaration shows that surprising synergism is obtained by combining both investigations, given the teachings of Rimm, it is not surprising or unexpected that circulating blood may contain cells that do not prove malignancy alone, but rather alert the scientist to a greater likelihood of malignancy.

Thus for the reasons above and those already of record, the rejection is maintained.

6. Claims 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsuhashi (US Pat. 5,976,797) in view of Ditkoff et al. (Surgery, Vol. 120, December 1996, pages 959-965) in view of Schmitz et al. (US Pat. 6,190,870, February 20, 2001) in view of Hoon et al (US Pat 6,057,105, May 2, 2000) as applied to 24, 26-27, 29-37, 44, 54, 61-66 above.

Neither Ditkoff nor Schmitz nor Hoon nor Rimm teach analyzing and identifying an anticancer therapy by administering an anticancer therapy to samples, and detecting the presence or expression of markers before and after to evaluate an anticancer therapy.

However, Mitsuhashi teaches a method for determining the cytoxoic effect of a compound by adding said compound to a sample, measuring mRNA present in sample and evaluating the cytotoxic effect of the compound. Mitsuhashi teaches studying vinblastine, cisplatin and mitomycin C.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Mitsuhashi for detecting cytotoxic effects of a anticancer compound such as cisplatin, for example, by detecting multiple markers in enriched and unenriched cultures. The ordinary artisan would have been motivated to have analyzed more than one mRNA for the reasons of specificity and reliability provided by Hoon. Determining the effect of an anticancer compound, or any compound, is accomplished by testing the nucleic acid expression prior to the administration of the compound, administering the compound and then comparing the expression following the compound administration. Therefore, the claimed methods are not novel with respect to the means in which an anticancer therapy is analyzed.

Response to Arguments

The response traverses the rejection. The response asserts that the combination of Ditkoff, Duffy and Hoon do not render the claims obvious. This argument has been

considered but is not convincing for the reasons above. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable over the art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
June 10, 2005